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REMARKS

Claims 1 and 3-17 are pending. Reconsideration of the present case is respectfully requested in light of the remarks below.

The pending claims are not obvious under 35 U.S.C. §103 over the cited Allen and Hellstrand references

Claims 1 and 3-17 are rejected under 35 U.S.C. §103(a) as being unpatentable over the combined disclosures of Allen (USPN 4,895,727, hereafter referred to as '727) and Hellstrand (WO 97/42968, hereafter referred to as '968). '727 discloses transmucosal agents comprising therapeutic agents, solvents, swelling agents and surficants. '968 discloses the use of histamine to augment the effects of other chemotherapeutic agents. The Examiner asserts that a skilled artisan would have been motivated to add the histamine of '968 to the transmucosal formulation of '727 to create a histaminic formulation that is easily dissolvable in the bloodstream. Applicant respectfully disagrees.

In establishing a *prima facie* case for obviousness, three criteria must each be met. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference or a combination of references must teach or suggest all of the limitations of the claims. M.P.E.P. §2143.

The disclosure of '727, entitled "Pharmaceutical vehicles for exhancing [sic] penetration and retention in the skin", is directed to transdermal and transmucosal preparations that feature chemical permeation enhancers that specifically do not increase blood flow to the area of application. The preparations deliver compounds to the skin and mucosal tissues. However, they are not meant to deliver compounds through the skin and mucosal tissues and into the bloodstream or the body, but instead are designed to create a "reservoir" of the delivered compound within the dermal or mucosal layer. *See* Column 1, lines 25-33. The preparations are specifically intended to be used with compounds for treatment of the dermal or mucosal layers that are systemically toxic to the individual being treated. By keeping most of the treatment compounds in the skin or mucosa and preventing the majority of the compound from entering the bloodstream, local treatment of skin or mucosal disorders with compounds that are normally toxic to the system can be achieved. *See* Column 1, lines 53-63; and Column 2, lines 14-23.

Histamine is known in the art to have a vasodilatory effect and to increase blood flow to the local area when applied. Use of histamine in the preparations of the '727 reference would work directly against the intended purpose of these preparations. The toxic treatment compounds, having entered the dermal layer at an accelerated rate due to the permeation-enhancing agents disclosed in the '727 reference, would have accelerated delivery into the body via the bloodstream due to the vasodilation caused by the histamine present in the composition. Thus, the presence of histamine in the compositions of '727 would antagonize the purpose for which the invention was created, and actually accelerate the delivery of toxic compounds systemically. Histamine is clearly not compatible with the compositions of the '727 reference as they are described and intended to be used.

In addition to histamine's incompatiblity with the envisioned use of the compositions of the '727 reference, the disclosure of the '727 reference does not support modifying the techniques described therein for use with histamine as described in the '968 reference. The '968 reference discloses the treatment of an individual with histamine to create stable circulating levels of histamine in the bloodstream of an individual, in order to augment treatment for a malignancy, a viral disease or a neoplastic disease. To practice the uses of histamine as described in the '968 reference, histamine must be delivered to a location within the body of a patient where the histamine is then free to circulate about the body, i.e. the bloodstream. The permiation enhancement agents of the '727 patent are designed specifically to retain the delivered compounds in the dermal and mucosal layers and to keep the delivered compounds away from the bloodstream. A person with skill in the art, given the disclosures of the '727 and '968 references, would conclude that the permiation agents described in the'727 reference are not desirable for delivering histamine transdermally or transmucosally to the bloodstream.

The combined disclosures of the '727 and '968 references fail to provide any of the criteria for a *prima facie* case of obviousness. They do not suggest or provide motivation to combine the teachings of the references. In fact, the disclosure of the '727 would discourage both the use of histamine in the compositions of '727 for the purposes described therein as well as the modification of the '727 compositions to deliver histamine to the bloodstream. The antagonistic activity of the dermally-retained permiability-enhancing agents of '727 and a vasodilatory agent such as histamine removes a reasonable expectation of success from the combination of the references. Lastly, the use of a permeation enhancing agent wherein the agent

is selected from the group consisting of histamine and histamine agonists is a limitation of the pending claims that is not taught or suggested in the references. Thus, the '727 and the '968 references, whether alone or combined, do not support a rejection of the claims due to *prima facie* obviousness under 35 U.S.C. §103.

The pending claims are not obvious under 35 U.S.C. §103 over the cited Fisher and Popovich references

The Examiner has noted that the '727 and '968 references lack any expressed disclosure of histamine as an agent that enhances permeability. The Examiner proceeds to cite two additional references, Fisher (USPN 3,880,996, hereafter referred to as '996) and Popovich et al (USPN 4,673,385, hereafter referred to as '385), which disclose the use of histamine as a vasodilation agent. The Examiner contends that the discussion of histamine as a vasodilator shows that the permeation enhancement of histamine was known as an inherent property of histamine and therefore the use of histamine for this purpose would have been obvious to a skilled artisan. Thus, the Examiner believes that the ability of histamine to enhance permeation is only due to its vasodilatory properties and that the description of the permeation enhancing ability of histamine is simply a description of an inherent feature of the compound in a new way. Applicant respectfully disagrees, and asserts that permeation enhancement and vasodilation are completely separate features.

As mentioned above, three criteria must be met in order to establish a *prima facie* case for obviousness. First, there must be some suggestion or motivation to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference or a combination of references must teach or suggest all of the limitations of the claims. M.P.E.P. §2143.

In the '996 reference, preparations for the transdermal delivery of an analgesic are disclosed. These preparations contain a polysiloxane to enhance the percutaneous absorption of the analgesic and a rubifacient agent. The purpose for including a rubifacient agent in topical analgesic compositions is described in the background section:

> "A substantial factor in whatever pain relief was achieved is believed to have been the rubefacient which provided the source of counter-irritation resulting in

localized heat sensation and concommitant psychological diversion or through the utilization of local anesthetics such as chloroform." (Col. 1, lines 22-27)

The compositions of '996 can also contain a local vasodilation agent such as histamine dihydrochloride. The sole purpose for the inclusion of the local vasodilation agent is to enhance the effect of the rubifacient compound. No mention is made of any effect that the local vasodilation agent may have on the polysiloxane permeation enhancement, on the absorption of the analgesic or on the analgesic's activity.

The '385 reference discloses a method of plasmapheresis, the clearing of undesired proteins from the plasma portion of the blood of an individual. The method utilizes the semi-permeable nature of the peritoneal membrane, a vascularized membrane located in the abdominal cavity. A fluid known as "plasmate", which is composed mostly of water and contains vasoactive agents, is injected into the peritoneal membrane, between the parietal and visceral (inner) portions of the membrane. The vasoactive agent in the plasmate will stimulate blood flow next to the membrane. Water will move out of the plasma, across the membrane and into the plasmate due to osmotic and hydrostatic forces. Proteins will also move across the membrane into the plasmate due to diffusion. However, blood cells and large structures such as platelets will remain behind in the blood. When the plasmate is removed from the peritoneal membrane, the individual's body is rid of the undesired plasma proteins that diffused into the plasmate. The presence of the vasoactive agent, such as histamine, serves only to increase blood flow to the peritoneal membrane. There is no disclosure or suggestion that the vasoactive agent affects the permeability of the peritoneal membrane in any way.

Semi-permeability is an inherent property of the peritoneal membrane that is exploited in the methods of the '385 patent; organopolysiloxanes are used to confer a semi-perimeable state to the dermis in the '996 patent. Neither of the two references discloses any information that would lead a skilled artisan to believe that histamine or any other vasoactive or vasodilatory agent would affect the permeability of the dermis, the peritoneal membrane or any other structure in the body. Neither reference provides any information to suggest the desirability of histamine over other vasodilatory agents in any formulation for enhancing transdermal or transmembrane delivery of compounds. Thus, there is no suggestion or motivation to modify the disclosures of these documents and no expectation of a successful increase in dermal or membrane permeability

with histamine or any other vasoactive or vasodilatory agent. As the references fail to disclose any effect that vasoactive or vasodilatory agents might have on dermal or membrane permeability, they fail to provide a reasonable expectation of successfully using histamine as an agent to enhance the transdermal or transmembrane delivery of a pharmaceutically active compound. Finally, the prior art fails to teach or suggest all of the limitations of the present claims since they lack any disclosure of enhanced dermal or membrane permeability with the use of histamine. Therefore the '996 and '385 prior art references fail to provide any of the three criteria required to establish a *prima facie* case of obviousness under 35 U.S.C. §103.

The pending claims are unobvious due to the lack of recognition of histamine as a permeation enhancing agent in the prior art

Since the Examiner believes that histamine's ability to enhance permeation is in fact just an attribute of its ability to dilate blood vessels, the Examiner concludes that the general conditions of the claims are disclosed in the prior art. Thus, the Examiner contends the the pending claims are obvious because the stated ranges for histamine concentrations in the compositions of the invention can be determined through routine experimentation. The Examiner also asserts that the claimed ranges and concentrations lack criticality and are therefore obvious in light of the prior art. The Examiner contends that a skilled artisan would have been motivated to combine the '968 and '727 references to create a transdermal histamine delivery system and would have used the teachings of '996 and '385 to create transmucosal delivery formulations wherein the formulation delivers its active agents more efficiently to the bloodstream. Applicant respectfully disagrees.

It is well established that before optimum ranges or values of a particular variable are characterized as a result of routine experimentation, the variable must first be recognized as a result-effective variable, *i.e.,* a variable which achieves a recognized result. *See* M.P.E.P §2144.05(II)(B) citing *In re Antonie*, 559 F.2d 618, 195 U.S.P.Q. 6 (C.C.P.A. 1977). In *In re Antonie*, the applicant had discovered an optimum ratio of tank volume to contactor area (0.12 gal./sq ft) which maximized treatment capacity of a wastewater treatment device. While the prior art disclosed tank volume and contactor area, the C.C.P.A. allowed the claims because the prior art did not recognize that treatment capacity is a function of the tank volume to contractor

ratio. In other words, the optimized ratio was not recognized in the art to be a result-effective variable.

The cited prior art references contain no suggestion that histamine could be used as a permeation enhancing agent and therefore do not recognize the permeation enhancement properties of histamine as a result-effective variable to be optimized. The Examiner maintains the position that any effect that histamine might have on the transdermal or transmucosal delivery of pharmacologically active agents to the body is simply a function of the vasodilation provoked by the application or injection of histamine. However, the prior art cited by the Examiner provides evidence that permeability is a separate factor from vasodilation and the resultant increases in local blood flow.

The '996 patent discloses compositions to deliver analgesic compounds transdermally. The reference discusses the inadequacy of prior art compositions, which contain an analgesic for pain relief and a rubifacient to create the sensation of heat. The reference notes that the delivery of the analgesics in the prior art formulations was insufficient and states that any pain relief from the application of prior art compositions most likely came from the distraction and psychological effects of the rubifacient or from the effects of topical anesthetics like chloroform. In the '996 patent, to create an improved composition, an organopolysiloxane agent that enhances the permeability of the dermal layer is added to analgesic formulations to increase the amount of analgesic that is delivered to the individual being treated. The '996 reference also mentions the inclusion of a local vasodilator agent, which is not present in the prior art formulations. However, the sole purpose for including this agent in the composition is to assist the function of the rubifacient. The improved nature of the composition is based on the enhanced delivery of the analgesic agent by increased permeability of the dermal layer, an effect that is produced by the polysiloxane agent. As increased permeability is the source of the improvement, the lack of a local vasodilator in some embodiments of this invention is evidence that histamine was not recognized as an agent that could enhance permeation of the dermal layer. Without recognition of this property of histamine in the reference, the motivation to perform experiments to determine the optimal dosage for exploiting this property of histamine could not have come from the disclosure of this reference.

The '385 reference discloses an improved system for performing plasmapheresis that uses a semi-permeable membrane from the patient's own body as a filtering mechanism. As

described in the reference, previous methods of plasmapheresis involved removing blood from the body, passing it through a filtering mechanism that allowed a fraction of the blood plasma to be separated from whole blood, and returning the whole blood to the body. The invention disclosed in the '385 patent uses a similar concept to achieve plasmapheresis, but does so *in vivo*, In this case, the prior art filtering mechanism has been replaced by layers of the peritoneal membrane. To increase the amount of blood passing by the membrane and the amount of material transferred from the blood plasma to the plasmate, a vasoactive agent is administered with the plasmate. The role of the vasoactive agent corresponds to the function of the pump in the prior art process, which is to facilitate the movement of whole blood across the filter membrane and thereby increase the diffusion rate of plasma fluid and proteins across the membrane by maintaining the concentration differential across the membrane. In neither process is it disclosed or suggested that the activity of the pump or the vasoactive agent alters in any way the inherent permeability of the filter or the membrane. The peritoneal membrane was selected for use in the *in vivo* plasmapheresis system because of its semi-permeable characteristics; no agents to increase or alter the permeability of the membrane are included, nor is the desirability of such an agent suggested. There is no disclosure in the '385 reference that any of the suggested vasoactive agents would impart an increased or altered level of permeability on any membrane or structure in the body. Thus, the '385 reference does not recognize the permeability enhancing properties of histamine as a result effective variable and its disclosure cannot be used as a basis for experiments intended to find the optimal dosage to exploit this variable.

As mentioned above, the disclosure of the '727 patent would lead a skilled artisan to conclude that use of histamine is incompatible with both the compositions as they are intended to be used and with the reservoir-creating permeability enhancers described therein. The '968 reference discloses the use of histamine supplementation to augment anti-cancer and anti-viral therapies and does not disclose nor suggest any role for histamine in vasodilation or permeation enhancement. Thus there is no motivation in these references to perform experiments to optimize the permeation enhancing properties of histamine through dosage variation.

The Examiner cites Nahoum (USPN 5,773,457, hereafter referred to as '457) in the Response to Arguments section on page 5 of the Final Office Action. The '457 reference discloses treatment of erectile dysfunction with various therapeutic agents, including histamine. The Examiner claims that this reference provides evidence that the use of histamine and

histamine agonists as permeation enhancing agents transdermally was a well-known property of histamine. The Examiner states that this reference discloses the use of histamine and histamine agonists "to enhance penetration of estrogen, testosterone and sex hormones through the skin and mucosa of sexual organs (abstract, examples)". The Examiner concludes that, given this information, a skilled artisan would be motivated to optimize the concentrations of histamine in order to maximize the permeation and delivery of therapeutic agents. Applicant respectfully disagrees.

The '457 reference discloses compounds for use as erectile agents in the treatment of sexual dysfunction, including histamine. The route of application for these agents, however, is injection into the base of the penis with a needle and syringe. Transdermal delivery of histamine to treat erectile dysfunction is discussed but the reference actually discourages use of this route of administration:

> "The existence of H_1 receptors in human skin, limits the concentration of histamine which may be used in a topical preparation. The *dose of histamine* which must be used *to cause expressive erection* will also cause the organ to show signs of local irritation. However, the use of topical preparations of histamine in combination with another agent which could reduce the amount of histamine needed would be of interest and is further described herein." (Column 3, Lines 45-52, emphasis added)

Further on in the text of the reference (Column 17, lines 34-48), topical preparations for the delivery of histamine to treat erectile dysfunction is described. The preparations are applied in a two-step process. In the first step, an ointment or cream that contains a carrier and a penetration enhancer is applied and allowed to remain for a few minutes. After wiping off the first preparation, a second ointment or cream containing the primary agent (e.g., histamine) would be applied. Also described is a two-step application system where an active agent is contained in the first ointment or cream while the second preparation contains "a second therapeutic agent, for example histamine or phentolamine". In both portions of the text that refer to transdermal delivery, histamine is referred to solely as an agent for the treatment of erectile dysfunction. This is also the case throughout the text, regardless of the route of application described. Other

properties of histamine, such as the vasodilatory effect or the enhancement of dermal permeability, are not disclosed or even suggested.

The Examiner claims that this reference discloses the use of histamine and histamine agonists "to enhance penetration of estrogen, testosterone and sex hormones through the skin and mucosa of sexual organs (abstract, examples)". However, a thorough reading of the entire text of the reference did not reveal a single reference to histamine or histamine agonists other than their singular role as erectogenic agents, to be used as the active ingredients in the treatment of sexual dysfunction. The use of carriers or permeation enhancers in envisioned in some embodiments of the invention, but the use of histamine or histamine agonists for these purposes is never disclosed or suggested. It is unclear from what evidence the Examiner drew his conclusions. In any case, the only role for histamine or histamine agonists disclosed or suggested by the '457 reference is as active agents to treat sexual dysfunction by inducing penile erections. There is no disclosure or suggestion of any other property of histamine or histamine agonists, except as skin irritants, as mentioned in the passage quoted above. With no disclosure or suggestion that histamine could serve as a permeation enhancer in the '457 reference, a skilled artisan would not be motivated by the reference to optimize the dose of histamine needed to produce the optimal level of permeation enhancement by histamine.

Conclusion

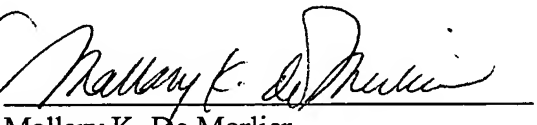
The Examiner has maintained his rejection of the claims under 35 U.S.C. §103 in light of four prior art references. However, none of the references disclose or suggest the permeation enhancing properties of histamine and two of the references actually teach away from or discourage the use of histamine in topical preparations. There is no information in the references that would lead one with skill in the art to have a reasonable expectation of successful permeation enhancement with the use of histamine. Without any evidence that histamine can enhance the permeation of or the entny into the dermal or mucosal layers by other agents, the references do not teach or suggest the limitations of the present claims, nor can the references' disclosures provide a basis for finding the optimal dosage of histamine as a permeation enhancer. For these reasons, Applicants respectfully request withdrawal of all rejections under 35 U.S.C. §103 and allowance of the application.

Applicant has endeavored to address all issues raised in the Final Office Action. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, the Examiner is respectfully requested to initiate the same with the undersigned. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/1/04

By: 

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